

Abdominal magnetic resonance imaging examination of Tibetan patients with abnormal iron metabolism and a preliminary study of correlations with blood cell analysis

Journal of International Medical Research

48(3) 1–7

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DOI: 10.1177/0300060520905483

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Abstract

Objective: The objective was to investigate factors influencing the high incidence of abnormal iron metabolism in a Tibetan population.

Methods: This was a retrospective observational study. Magnetic resonance imaging and blood analysis of 363 Tibetan patients were performed and patients divided into normal and abnormal groups based on the clinical diagnostic standard. The upper limit of normal liver iron content was 50 $\mu\text{mol/g}$. We analyzed the association between abnormal iron metabolism and blood cell indicators using the Spearman rank correlation test.

Results: In male patients, differences in mean corpuscular hemoglobin (MCH) and MCH concentration in blood between the normal and abnormal groups were significant. Abnormal iron metabolism in male patients was positively correlated with MCH and MCH concentration. In female patients, differences in erythrocytes, hemoglobin, and hematocrit levels between the two groups were significant. Erythrocyte counts and hemoglobin and hematocrit levels of female patients were positively correlated.

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Conclusion: Iron overload in male patients was correlated with an increase in MCH and MCH concentration, and that in female patients was correlated with levels of erythrocytes, hemoglobin, and hematocrit. The incidence rate of iron overload was higher in males than in females and was correlated with age in this Tibetan population.

Keywords

MRI, abnormal iron metabolism, blood cell analysis, Tibetan people, liver, imaging

Date received: 18 July 2019; accepted: 15 January 2020

Introduction

Systemic iron overload is a disorder characterized by high levels of plasma iron with subsequent deposition in multiple organs such as liver, pancreas, heart, pituitary gland, and joints.^{1–3} Histologically, excess iron in the body is stored primarily in hepatocytes and macrophages.⁴ Hence, abnormal iron metabolism first involves the liver and spleen. The liver is the main location for iron storage and is the earliest and most critical organ for iron deposition.⁵ Excess accumulation of iron may lead to life-threatening complications, including liver fibrosis, cirrhosis, liver failure, and hepatocellular carcinoma.⁶

The gold standard method to measure liver iron concentration is a biopsy; however, a liver biopsy is invasive and susceptible to sample variability from uneven hepatic iron concentration.⁷ In recent years, radiological technologies, including computed tomography and magnetic resonance imaging (MRI), are better able to reflect the degree of organ iron overload and monitor treatment noninvasively and quantitatively.^{8–11} MRI has recently been favored as an initial diagnostic test for assessing iron overload via the T2* parameter, an exponential decay constant that can be calculated from a single gradient-echo sequence with multiple echo times. T2* sequences have demonstrated high sensitivity in detecting hepatic iron deposition, even in

the early stages of the disease, and T2* values correlate well with liver iron concentrations derived from biopsy.^{12–14}

At present, few etiological studies have been conducted on the high incidence of abnormal iron metabolism among plateau people. Hence, the pathogenesis of abnormal iron metabolism in Tibetan people remains unclear. The present study aimed to investigate the factors underlying the high incidence rate of abnormal iron metabolism in the Tibetan population and to conduct a preliminary study on the correlation between abdominal MRI manifestations and blood cell analysis.

Patients and methods

This study was conducted in accordance with the Declaration of Helsinki and in compliance with ethical guidelines. The study was approved by the Ethics Committee of West China Hospital, Sichuan University. Written informed consent was obtained from the participants or their guardians.

Study objective

This was a retrospective observational study. Imaging and blood cell analysis data were collected from 363 patients in Tibet who underwent middle and upper abdominal MRI examinations in our hospital from January 2014 to December 2017.

The inclusion criteria were (1) Tibetan; (2) patients who underwent middle and upper abdominal MRI examinations and blood cell analysis; (3) patients who had an abnormal MRI and met the diagnostic standard for clinical abnormal iron metabolism (transferrin saturation $>45\%$ and serum ferritin >250 and >200 ng/mL for men and women, respectively).^{15–17} The exclusion criteria were (1) patients with serious image motion artifacts in which an analysis could not be made; (2) patients with large space-occupying lesions of the liver, spleen, or pancreas in which the excessively large focus affected assessment and analysis of MRI signal.

MRI examination

MRI examinations were performed on a 3.0 T system (Philips, Best, Netherlands) with 16-channel body phased-array coils. The patient was placed in the supine position and an MRI plain scan sequence was taken, including T1-weighted image (WI), T2WI, T2WI spectral attenuated inversion recovery (SPAIR), multi-echo T2*WI, and in/out phase sequence. We used a signal intensity ratio method based on T1 and T2* contrast imaging without gadolinium, as established by Gandon et al. at Rennes University.¹⁸ For liver iron content (LIC) measured by MRI performance, the upper limit was set at $50 \mu\text{mol/g}$ for this study; LIC values $>50 \mu\text{mol/g}$ were considered abnormal.

Statistical analysis

SPSS version 22.0 (IBM Corp., Armonk, NY, USA) was used for data analysis. Measurement data of normally distributed data were expressed as mean \pm standard deviation (SD), data of skewed distributions were expressed in medians, and enumeration data were expressed as frequencies. Continuous variables were

compared between the two groups by using the two independent samples *t*-test. Discontinuous variables were compared by χ^2 test. Associations between abnormal iron metabolism and indicators of blood cells were analyzed using the Spearman rank correlation test. $P < 0.05$ was considered statistically significant.

Results

MRI signals

Of the 363 Tibetan patients, 268 were male. The age (mean \pm SD) of Tibetan patients in the normal and abnormal groups was 46.14 ± 12.99 and 52.70 ± 10.79 years, respectively ($P < 0.001$). The age of male patients in the normal and abnormal groups was 47.68 ± 12.64 and 51.78 ± 10.78 years, respectively ($P = 0.007$). The age of female patients in the normal and abnormal groups was 43.78 ± 13.30 and 56.93 ± 9.92 years, respectively ($P < 0.001$). Representative images from the MRI examinations are shown in Figure 1.

Blood cell analyses

In male patients, significant differences in mean corpuscular hemoglobin ($P = 0.016$) and mean corpuscular hemoglobin concentration ($P = 0.006$) were found in patients with normal and abnormal MRI signals. However, erythrocyte counts, hemoglobin and hematocrit levels, and mean corpuscular volume did not differ significantly between the two groups (Table 1).

In female patients with normal and abnormal MRI signals, we found significant differences in erythrocyte counts and hemoglobin and hematocrit levels ($P = 0.005$, $P = 0.001$, and $P = 0.001$, respectively). However, mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration did not differ between normal and abnormal groups (Table 1).

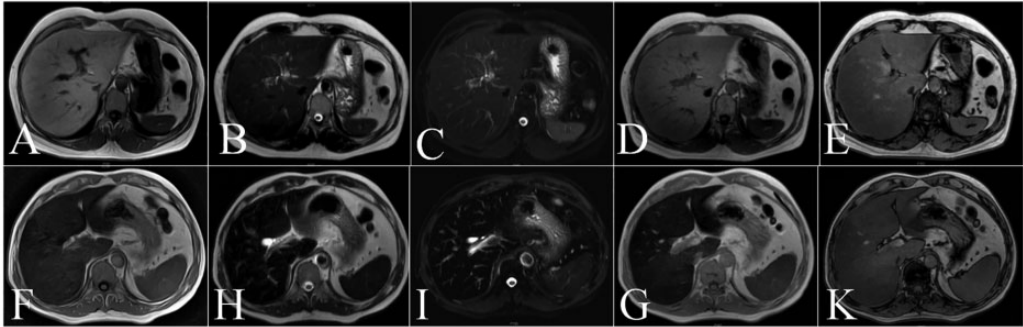


Figure 1. Normal abdominal and iron overload images by MRI: (A) TIWI normal abdominal image; (B) T2WI normal abdominal image; (C) T2WI SPAIR normal abdominal image; (D) in-phase normal abdominal image; (E) out-phase normal abdominal image; (F) TIWI iron overload image; (H) T2WI iron overload image; (I) T2WI SPAIR iron overload image; (G) in-phase iron overload image; (K) out-phase iron overload image. MRI, magnetic resonance imaging; TIWI, T1-weighted image; T2WI, T2-weighted image; SPAIR, spectral attenuated inversion recovery.

Table 1. Blood cell analysis of patients in the normal and abnormal MRI groups.

	Grouping by MRI signal		P-value
	Normal group	Abnormal group	
Male patients	(n = 84)	(n = 184)	
Erythrocyte count ($10^{12}/L$)	5.07 (2.53–9.83)	5.06 (3.07–7.29)	0.927
Hemoglobin (g/L)	152.05 (54–207)	156.89 (94–230)	0.231
Hematocrit (%)	45.07 (18.3–64.1)	45.86 (29.3–69.8)	0.535
Mean corpuscular volume (fL)	89.61 (65.2–107.6)	90.64 (29.7–103.6)	0.151
Mean corpuscular hemoglobin (pg)	30.30 (20.0–35.8)	31.12 (26.2–36.1)	0.016*
Mean corpuscular hemoglobin concentration (g/L)	336.55 (247–360)	341.71 (249–378)	0.006*
Female patients	(n = 55)	(n = 40)	
Erythrocyte count ($10^{12}/L$)	4.22 (2.56–5.10)	4.53 (2.72–5.50)	0.005*
Hemoglobin (g/L)	123.12 (72–160)	135.10 (47–163)	0.001*
Hematocrit (%)	37.42 (22.7–46.6)	40.45 (18.6–48.0)	0.001*
Mean corpuscular volume (fL)	88.96 (69.6–104.4)	89.21 (63.5–108.5)	0.815
Mean corpuscular hemoglobin (pg)	29.17 (19.0–34.9)	29.68 (16.00–35.00)	0.579
Mean corpuscular hemoglobin concentration (g/L)	327.22 (272–360)	332.25 (253–361)	0.092

MRI, magnetic resonance imaging.

* $P < 0.05$.

Correlation of abnormal iron metabolism and blood cell indicators

In male patients, we found that abnormal iron metabolism (transferrin saturation

>45% and serum ferritin >250 ng/mL) was positively correlated with mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration. In male patients, the single factor correlation

analysis showed that abnormal iron metabolism was positively correlated with mean corpuscular hemoglobin ($r=0.147$, $P=0.016$) and mean corpuscular hemoglobin concentration ($r=0.169$, $P=0.006$). However, the correlation coefficients were low (<0.5). Correlations of abnormal iron metabolism with erythrocyte counts, hemoglobin and hematocrit levels, and mean corpuscular volume were not significant.

In female patients, abnormal iron metabolism was positively correlated with erythrocyte count and hemoglobin and hematocrit levels. However, the correlation coefficients were low (<0.5). Correlations of abnormal iron metabolism with mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration were not significant.

Discussion

The incidence rate of iron overload was high in the Tibetan population studied here. Previous studies have found that the high incidence of iron overload in Tibetan people is correlated with oxygen deficiency.¹⁹ Because oxygen deficiency in the body requires more hemoglobin to meet the oxygen demand, the demand for erythropoietin will increase. Researchers have proposed that oxygen deficiency may promote an increase of erythropoietin by inducing the transcription factor hypoxia-inducible factor.²⁰ However, the pathophysiology of such an interaction remains unknown. Because plateau anoxia and drying can increase the brittleness of the erythrocyte membrane, the life span of erythrocytes is shortened, erythrocyte destruction is increased, and the metabolism product from senescent erythrocytes promotes an increase of hematopoietic and erythroid cells.²¹ Previous studies have shown that anoxia can be relieved by taking iron supplements.²² Therefore, when the body is in an oxygen-deficient environment, the

oxygen deficiency would certainly increase iron absorption and utilization to meet the needs of the body. We found significant differences in erythrocyte counts and hemoglobin and hematocrit levels of female patients with normal and abnormal MRIs. However, in male patients in our study, significant differences were found in mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration between the two groups.

In addition to the effect of the oxygen-deficient environment in plateaus, iron metabolism is correlated with living habits, such as drinking and long-term meat eating. The prevalence of abnormal iron metabolism among Tibetan patients increases with increasing age, regardless of sex. This may be because the oxygen demand of the body increases with age. However, cardiopulmonary function weakens and oxygen uptake decreases with increasing age. Furthermore, slower metabolism would cause deposition of iron in the body. The incidence of abnormal iron metabolism was higher in men than in women in our study, which may be due to differences in the secretion level of estrogen and androgen in men and women.²³ In addition, abnormal iron metabolism is correlated with cardiopulmonary function, the endurance capacity of oxygen deficiency, and living habits. This needs to be proven through further studies.

Although Tibetan people living on the plateau for long periods suffer from abnormal iron metabolism because of the chronic oxygen-deficient environment and have abnormal organ MRI manifestations, the male patients in our group mainly showed an increase in mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration, whereas female patients manifested changes in erythrocyte counts and levels of hemoglobin and hematocrit. At present, there are few studies on iron metabolism among people living on the

Tibetan plateau, and the specific factors influencing the high incidence of abnormal iron metabolism in Tibetans have been rarely reported.

Conclusion

Iron overload in Tibetan men was correlated with increases in mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration, whereas iron overload in Tibetan women was correlated with erythrocyte counts and levels of hemoglobin and hematocrit. The incidence of iron overload was higher in men than in women and was correlated with age.


Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Funding

This study was supported by Natural Science Foundation of Tibet (No. XZ2017ZRG-92).

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References

1. Serai SD and Trout AT. Can MR elastography be used to measure liver stiffness in patients with iron overload? *Abdom Radiol (NY)* 2019; 44: 104–109.
2. Sarigianni M, Liakos A, Vlachaki E, et al. Accuracy of magnetic resonance imaging in diagnosis of liver iron overload: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2015; 13: 55–63.e5.
3. Shen Y, Zheng C, Tan Y, et al. MagA increases MRI sensitivity and attenuates peroxidation-based damage to the bone-marrow haematopoietic microenvironment caused by iron overload. *Artif Cells Nanomed Biotechnol* 2018; 46: S18–S27.
4. Ackerman Z, Pappo O, Link G, et al. Liver toxicity of thioacetamide is increased by hepatocellular iron overload. *Biol Trace Elem Res* 2015; 163: 169–176.
5. Cancado R, Watman NP, Lobo C, et al. Assessment of liver and cardiac iron overload using MRI in patients with chronic anemias in Latin American countries: results from ASIMILA study. *Hematology* 2018; 23: 676–682.
6. Hassan MG, Paul TK, Fernando FS, et al. Hepatic iron overload identified by magnetic resonance imaging-based T2* is a predictor of non-diagnostic elastography. *Quant Imaging Med Surg* 2019; 9: 921–927.
7. Seeff LB, Everson GT, Morgan TR, et al. Complication rate of percutaneous liver biopsies among persons with advanced chronic liver disease in the HALT-C trial. *Clin Gastroenterol Hepatol* 2010; 8: 877–883.
8. Tang H, Jensen JH, Sammet CL, et al. MR characterization of hepatic storage iron in transfusional iron overload. *J Magn Reson Imaging* 2014; 39: 307–316.
9. Simchick G, Liu Z, Nagy T, et al. Assessment of MR-based R2* and quantitative susceptibility mapping for the quantification of liver iron concentration in a mouse model at 7T. *Magn Reson Med* 2018; 80: 2081–2093.
10. Pirasteh A, Yuan Q, Hernando D, et al. Inter-method reproducibility of biexponential R2 MR relaxometry for estimation of liver iron concentration. *Magn Reson Med* 2018; 80: 2691–2701.
11. Felker ER, Choi KS, Sung K, et al. Liver MR elastography at 3 T: agreement across pulse sequences and effect of liver R2* on image quality. *AJR Am J Roentgenol* 2018; 211: 588–594.
12. Wood JC. Estimating tissue iron burden: current status and future prospects. *Br J Haematol* 2015; 170: 15–28.
13. Wood JC. Use of magnetic resonance imaging to monitor iron overload. *Hematol Oncol Clin North Am* 2014; 28: 747–764.
14. Tolouian R, Mulla ZD, Diaz J, et al. Liver and cardiac iron deposition in patients on maintenance hemodialysis by magnetic resonance imaging T2. *Iran J Kidney Dis* 2016; 10: 68–74.
15. Leitch HA. Optimizing therapy for iron overload in the myelodysplastic syndromes:

- recent developments. *Drugs* 2011; 71: 155–177.
16. Wunderlich AP, Cario H, Juchems MS, et al. Noninvasive MRI-based liver iron quantification: methodic approaches, practical applicability and significance. *Rofo* 2016; 188: 1031–1036.
 17. Kritsaneepaiboon S, Ina N, Chotsampancharoen T, et al. The relationship between myocardial and hepatic T2 and T2* at 1.5T and 3T MRI in normal and iron-overloaded patients. *Acta Radiol* 2018; 59: 355–362.
 18. Gandon Y, Olivie D, Guyader D, et al. Non-invasive assessment of hepatic iron stores by MRI. *Lancet* 2004; 363: 357–362.
 19. Sun SY, Guo YH, Sun ZM, et al. Analysis of HFE and Non-HFE mutations in a Tibet cohort with iron overload. *Zhongguo Shi Yan Xue Ye Xue Za Zhi* 2019; 27: 618–622.
 20. Zhou YF, Wu XM, Zhou G, et al. Cystathionine beta-synthase is required for body iron homeostasis. *Hepatology* 2018; 67: 21–35.
 21. Borriello A, Caldarelli I, Speranza MC, et al. Iron overload enhances human mesenchymal stromal cell growth and hampers matrix calcification. *Biochim Biophys Acta* 2016; 1860: 1211–1223.
 22. Ganz T and Nemeth E. Heparin and iron homeostasis. *Biochim Biophys Acta* 2012; 1823: 1434–1443.
 23. Tipirneni-Sajja A, Krafft AJ, McCarville MB, et al. Radial ultrashort TE imaging removes the need for breath-holding in hepatic iron overload quantification by R2* MRI. *AJR Am J Roentgenol* 2017; 209: 187–194.